JOC*Article*

Combined Directed Ortho Metalation/Cross-Coupling Strategies: Synthesis of the Tetracyclic A/B/C/D Ring Core of the Antitumor Agent Camptothecin

Tam Nguyen, Markus A. Wicki,[‡] and Victor Snieckus*,[†]

The Guelph-Waterloo Centre for Graduate Work in Chemistry, Department of Chemistry, University of Waterloo, Waterloo, ON, Canada N2L 3G1

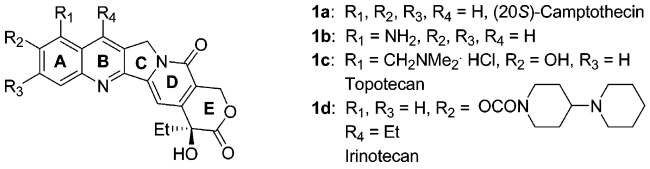
snieckus@chem.queensu.ca

Received January 19, 2004

A convergent synthesis of the A/B/C/D ring fragment **5** of camptothecin using a combination of directed ortho metalation and Negishi cross-coupling is described. The key features of the synthetic sequence are an anionic ortho-Fries rearrangement (**10** → **12**), a Negishi cross-coupling (**7** → **6**), and a terminal modified von Braun reaction (**16** → **5**) that leads to tetracyclic derivative **5** in 7 steps and 11% overall yield.

Introduction

(20*S*)-Camptothecin (**1a**), one of the most potent antitumor natural products, was first isolated in 1966 from *Camptotheca acuminata* Nyssaceae by Wall et al.[1,2] Its unusual structure and intriguing speculative biosynthetic pathway[3] stimulated immediate and intense synthetic activity worldwide,[4,5] which subsequently precipitously declined due to the finding of discouraging biological activity data of **1a**[5] showing serious toxic side effects. In the past 15 years, renewed synthetic interest in **1a** and analogues[6] evolved due to findings that substituted derivatives of **1a** such as 9-aminocamptothecin (**1b**),[7] 9-((dimethylamino)methyl)-10-hydroxycamptothecin (Topotecan, **1c**),[8] and Irinotecan (**1d**)[9] show low overall toxicity, higher solubility, and still impressive in vivo activity against certain solid tumors. In fact, Topotecan **1c** and Irinotecan **1d** were recently approved by the FDA for the treatment of ovarian cancer and small-cell lung cancer[10] and refractory colorectal cancer, respectively.[11]



Alkaloids structurally related to camptothecin (**1a**) such as homocamptothecin (**2**),[12g,13] mappicine (**3**),[14,15] and mappicine ketone (**4**)[15] are also of clinical relevance. Homocamptothecin (**2**) and its derivatives show similar therapeutic activities to the camptothecins (**1**). The E-ring lactone in **1a** easily hydrolyzes at physiological pH leading to the biologically inactive carboxylate, an inherent deficiency of the parent compound **1a**.[16] In the E-ring lactone of **2** the tertiary alcohol and the lactone carbonyl are separated by a methylene spacer. It was found in bioassays that the longevity of activity of **2** was increased compared to that of **1a**.[17] Mappicine ketone (**4**) has been identified as an antiviral lead compound with selective

[†] Present address: Department of Chemistry, Queen's University, Kingston, ON, Canada K7L 3N6.

[‡] Present address: Corporate Research & Development Laboratory, 3M Canada Company, P.O. Box 5757, London, ON, Canada N6A 4T1.

(1) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.

(2) For other natural sources of camptothecin and its derivatives, see: Das, B.; Madhusudhan, P.; Reddy, P. V.; Anitha, Y. *Indian J. Chem.* **2001**, *40B*, 453.

(3) Brown, R. T.; Liu, J.; Santos, C. A. M. *Tetrahedron Lett.* **2000**, *41*, 859.

(4) Winterfeldt, E. *Recent Dev. Chem. Nat. Carbon Compds*. **1975**, *6*, 11−34.

(5) Nicholas, A. W.; Wani, M. C.; Manikumar, G.; Wall, M. E.; Kohn, K. W.; Pommier, Y. *J. Med. Chem.* **1990**, *33*, 972.

(6) Du, W. *Tetrahedron* **2003**, *59*, 8649.

(7) Giovanella, B. C.; Stehlin, J. S.; Wall, M. E.; Wani, M. C.; Nicholas, A. W.; Liu, L. F.; Silber, R.; Potmesil, M. *Science* **1989**, *246*, 1046.

(8) Kingsbury, W. D.; Boehm, J. C.; Jakas, D. R.; Holden, K. G.; Hecht, S. M.; Gallagher, G.; Caranfa, M. J.; McCabe, F. L.; Faucette, L. F.; Johnson, R. K.; Hertzburg, R. P. *J. Med. Chem.* **1991**, *34*, 98.

(9) Sawada, S.; Okajima, S.; Aiyama, R.; Nokata, K.; Furuta, T.; Yokokura, T.; Sugino, E.; Yamaguchi, K.; Miyasaka, T. *Chem. Pharm. Bull.* **1991**, *39*, 1446.

(10) Herzog, T. J. *Oncologist* **2002**, *7* (Suppl. 5), 3.

(11) Henegar, K. E.; Ashford, S. W.; Baughman, T. A.; Sih, J. C.; Gu, R.-L. *J. Org. Chem.* **1997**, *62*, 6588.

(12) (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863. (b) Curran, D. P.; Ko, S.-B.; Josien, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2683. (c) Curran, D. P.; Liu, H.; Josien, H.; Ko, S.-B. *Tetrahedron* **1996**, *52*, 11385. (d) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67. (e) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908. (f) Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2923. (g) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215. (h) Du, W.; Curran, D. P. *Synlett* **2003**, 1299.

(13) Gabarda, A. E.; Du, W.; Isarno, T.; Tangirala, R. S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 6329.

(14) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **1998**, *120*, 1218.

(15) Comins, D. L.; Saha, J. K. *J. Org. Chem.* **1996**, *61*, 9623.

(16) Turner, K. *Org. Process Res. Dev.* **2004**, *8*, 553.

(17) Blagg, B. S. J.; Boger, D. L. *Tetrahedron* **2002**, *58*, 6343 and references therein.

10.1021/jo049890h CCC: $27.50
Published on Web 10/21/2004

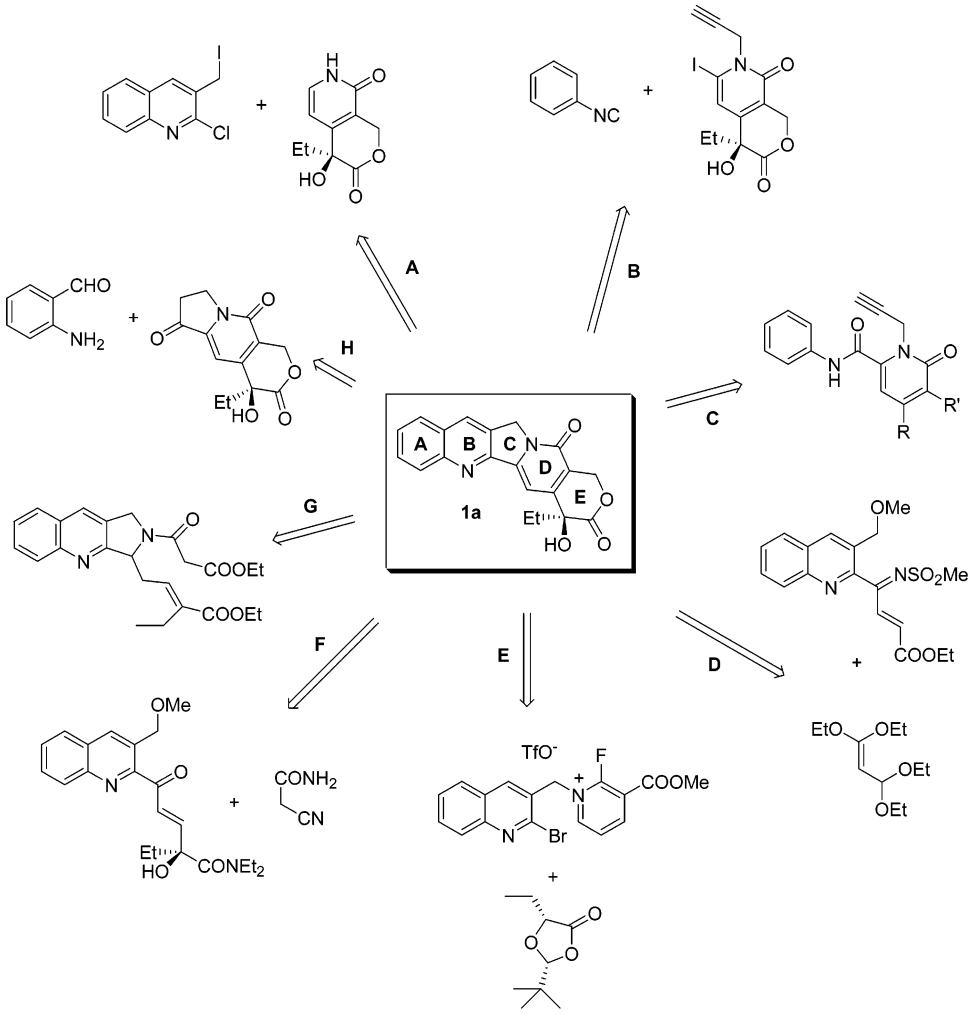
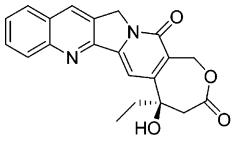
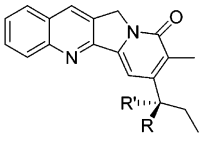


FIGURE 1. Selected strategies for the synthesis of camptothecin.

activities against herpes viruses HSV-1 and HSV-2 and human cytomegalovirus.[18]



2: Homocamptothecin



3: R=OH, R'=H (Mappicine)
4: R, R'=O (Mappicine ketone)

The antitumor activity of the camptothecins is now accepted to be associated with the inhibition of DNA relaxation by specific interference of the function of DNA topoisomerase I.[19,20] Interestingly, it has been shown that the tetracyclic A/B/C/D ring core of **1a** functions as the key binding site to DNA.[21]

Camptothecin and its analogues have provided a rich playing field for development of convergent total synthesis strategies. To date, the shortest asymmetric synthesis of **1a** by Comins involves the formation of the C-ring by connecting the A/B- and D/E-fragments via an *N*-alkylation and a key intramolecular Heck ring closure reaction (Figure 1, A).[22] Curran devised an imaginative strategy in which the appropriately functionalized A- and D/E-fragments (Figure 1, B) participate in a free-radical cascade leading to the formation of the B- and C-rings of **1a**.[12] A different concomitant formation of the B- and C-rings was reported by Fortunak using an efficient intramolecular Diels−Alder reaction (Figure 1, C) that is now used on an industrial scale.[23] Boger devised an approach in which a D-ring forming intermolecular Diels−Alder process precedes a C-ring cyclization (Figure 1, D).[17] The key features of an inventive strategy[24] by Bosch consisted of an intramolecular radical cyclization to form the C-ring followed by asymmetric construction of the E-ring using enolate chemistry (Figure 1, E).

(18) (a) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623. (b) Pendrak, I.; Wittrock, R.; Kingsbury, W. D. *J. Org. Chem.* **1995**, *60*, 2912.

(19) Berry, D. E.; MacKenzie, L.; Shultis, E. A.; Chan, J. A. *J. Org. Chem.* **1992**, *57*, 420.

(20) Fang, S.-D.; Wang, L.-K.; Hecht, S. M. *J. Org. Chem.* **1993**, *58*, 5025.

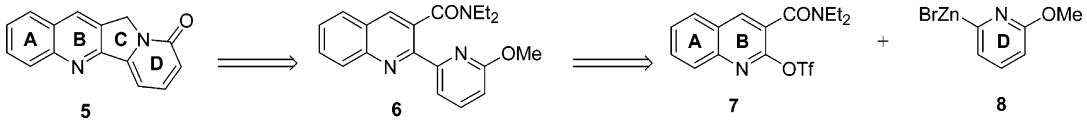
(21) Perzyna, A.; Marty, C.; Facompré, M.; Goossens, J.-F.; Pommery, N.; Colson, P.; Houssier, C.; Houssin, R.; Hénichart, J.-P.; Bailly, C. *J. Med. Chem.* **2002**, *45*, 5809.

(22) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255 and references therein.

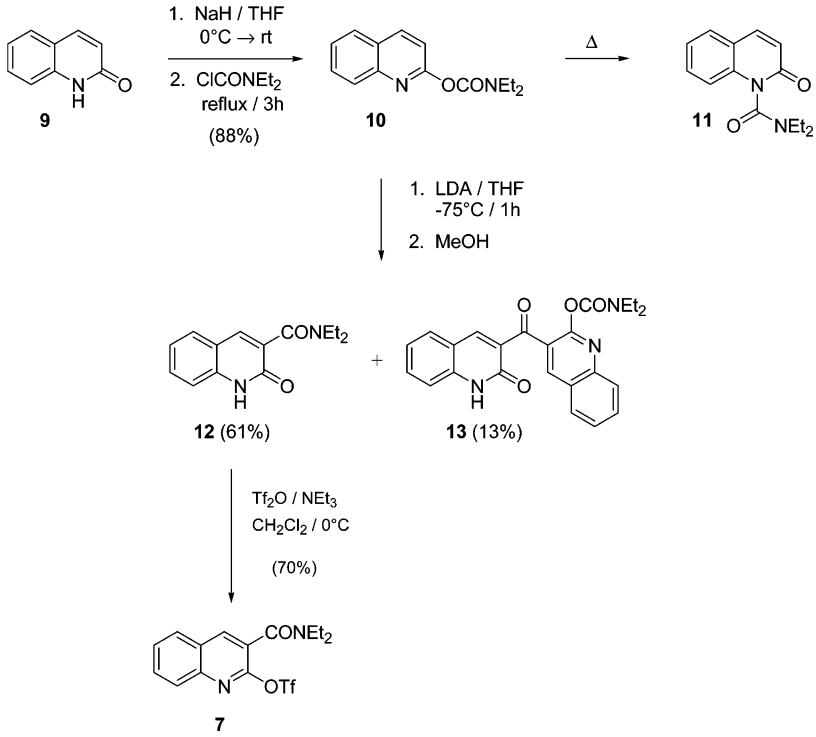
(23) Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Sisti, N. J.; Wood, J. L.; Zhuang, Z.-P. *Tetrahedron Lett.* **1996**, *37*, 5679.

(24) Bennasar, M.-L.; Zulaica, E.; Juan, C.; Alonso, Y.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 7465.

SCHEME 1



SCHEME 2



Intermolecular[25] (Figure 1, F) and intramolecular[26] (Figure 1, G) Michael addition reactions by Ciufolini and Chavan, respectively, were utilized for the D-ring construction of **1a**. Finally, in a route that has been widely traveled from the beginning of camptothecin synthetic work, a classical Friedlander reaction of 2-aminobenzaldehyde (A-ring) with the assembled C/D/E-ring framework (Figure 1, H) was used by Henegar for B-ring annelation of **1a**.[11]

Herein, we report a new synthesis of the A/B/C/D-ring core **5**[27] of **1a** using a combined directed ortho metalation (DoM)−transition metal catalyzed cross-coupling tactic.[28] Thus, the construction of **5** is based on the initial coupling of **7**, prepared by anionic Fries rearrangement,[29] with the organozinc species **8** to afford **6**, which, by simple functional group manipulation−cyclization leads to C-ring formation (Scheme 1).

Results and Discussion

As an appropriate precursor of coupling partner **7**, 2-quinolone (**9**) (Scheme 2), prepared in sizable quantities following Henze's procedure,[30] was converted into the *O*-carbamate **10** by treatment with sodium hydride and diethyl carbamoyl chloride in refluxing THF[31] followed by purification by flash chromatography on SiO_2. In an alternative purification of carbamate **10** via short path distillation, a clean thermal 1,3-carbamoyl rearrangement was observed to form urea **11**.[32] As reported by Queguiner,[31] treatment of carbamate **10** with LDA resulted in, even at −75 °C, C-3 metalation−anionic Fries rearrangement to give the 3-amidoquinolone **12**. However, in contrast to the observations of Queguiner, apart from **12** (61%), the self-condensation product **13** was also isolated in 13% yield. When the reaction was carried out at −42 °C, compound **13** was not formed and the yield of the desired rearrangement product **12** increased to 71%. The increased selectivity favoring the intramolecular rearrangement at higher temperature may be rationalized by the difference in temperature dependence of a

(25) Ciufolini, M. A.; Roschangar, F. *Angew. Chem., Int. Ed. Engl.* **1990**, *35*, 1692. Ciufolini, M. A.; Roschangar, F. *Tetrahedron* **1997**, *32*, 11049. Ciufolini, M. A.; Roschangar, F. *Targets Heterocycl. Syst.* **2000**, *4*, 25.

(26) Chavan, S. P.; Venkatraman, M. S. *Tetrahedron Lett.* **1998**, *39*, 6745.

(27) Compound **5** has been previously prepared, see: (a) Kametani, T.; Nemoto, H.; Takeda, H.; Takano, S. *Tetrahedron* **1970**, *26*, 5753. (b) See ref 12a. (c) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 58.

(28) For a recent review, see: (a) Anctil, E.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (b) Anctil, E.; Snieckus, V. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Diederich, F., de Meijere, A., Eds., 2004, in press.

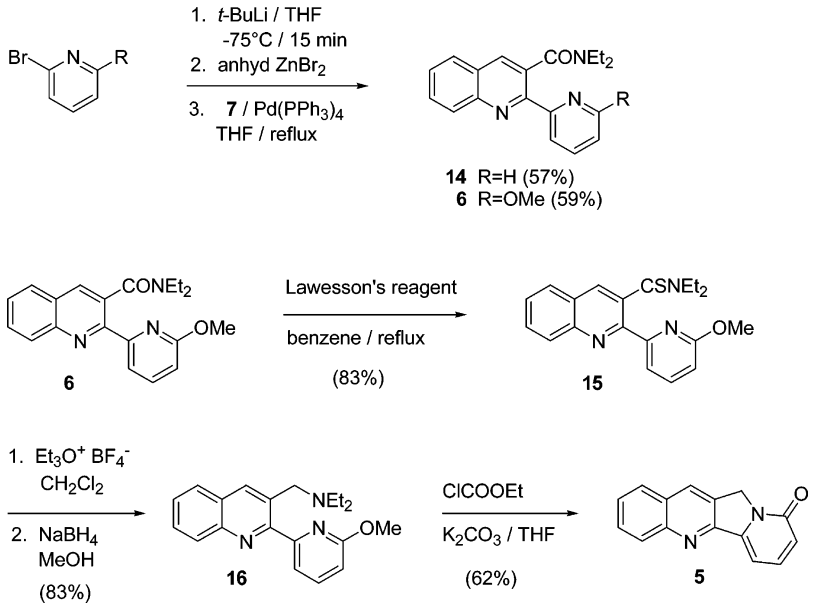
(29) Sibi, M.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935.

(30) Henze, M. *Chem. Ber.* **1936**, *69*, 1566.

(31) Jacquelin, J. M.; Robin, Y.; Godard, A.; Queguiner, G. *Can. J. Chem.* **1988**, *66*, 1135.

(32) (a) For an analoguous thermal carbonate−carbamate rearrangement, see: Nagata, T.; Koide, Y.; Nara, K.; Itoh, E.; Arisawa, M. *Chem. Pharm. Bull.* **1996**, *44*, 451. (b) For the equilibrium of *N*-acetyl-2-pyridone and 2-acetoxypyridine, see: McKillop, A.; Zelesko, M. J.; Taylor, E. C. *Tetrahedron Lett.* **1968**, *48*, 4945. Fleming, I.; Philippides, D. *J. Chem. Soc. C* **1970**, 2426. (c) Miah. M. A. J. Ph.D. Thesis, University of Waterloo, 1985.

SCHEME 3



uni- vs. bimolecular reaction. To complete the synthesis of the A/B-fragment, the quinolone **12** was transformed into the triflate **7** with use of standard conditions.

As a model reaction, the cross-coupling reaction between triflate **7** and 2-bromopyridine,[33] representing the D-ring fragment, was undertaken (Scheme 3) with use of the Negishi protocol[34] with $Pd(PPh_3)_4$ as catalyst and provided the biaryl **14** in satisfactory yield (57%). With this procedure, 2-bromo-6-methoxypyridine, prepared from 2,6-dibromopyridine (86% yield),[35] was sequentially treated with 2 equiv of *t*-BuLi at −78 °C and anhydrous $ZnBr_2$. The resulting organozinc species **8** was subjected to the Pd^0-catalyzed cross-coupling procedure with triflate **7** to afford the biaryl **6** in 59% yield.

To avoid complications of reduction of π-deficient heterocyclic rings, the biaryl **6** was subjected to the mild reduction protocol of Raucher.[36] Thus, **6** was converted with use of Lawesson's reagent into the corresponding thioamide **15**, which, upon sequential ethylation with ethyl-Meerwein salt and reduction with $NaBH_4$, was transformed into the tertiary amine **16** in 83% yield. The final cyclization of **16** to the tetracycle **5**[27] was achieved in 62% yield via a modified von Braun reaction with ethyl chloroformate and potassium carbonate.[37] Compound **5** was found to be identical by comparison of physical and spectroscopic properties with those reported (see the Experimental Section).

Thus, the tetracyclic A/B/C/D-ring system **5** of camptothecin (**1a**) has been synthesized from quinolone **9** in 7 steps and 11% overall yield, which represents a valuable alternative to previously achieved syntheses (7 steps, 6%;[27a] 2 steps, 27%;[27b] and 5 steps, 17%[27c]). The simplicity of the steps, the ready availability of starting materials of both A/B- and D-ring fragments by DoM chemistry, and the potential further modification of ring D in **5**, taken in sum, offer consideration of additional avenues for synthetic excursions in the camptothecin field.

Experimental Section

***N,N*-Diethyl *O*-(Quinolyl-2) Carbamate (10).** To a suspension of NaH (959 mg, 60% in mineral oil, 24.0 mmol) in anhydrous THF (45 mL) was added **9**[30] (2.88 g, 19.8 mmol) portionwise at room temperature under N_2 atmosphere. The greenish suspension was stirred at room temperature for 30 min and then $ClCONEt_2$ (3.75 g, 27.6 mmol) was added via syringe. The reaction mixture was refluxed for 2 h. Since TLC showed only about 50% conversion, more $ClCONEt_2$ (3.75 g, 27.6 mmol) was added and the mixture was stirred for an additional hour. The reaction mixture was cooled in ice and carefully treated with saturated aq NH_4Cl (20 mL). The aqueous layer was separated and extracted with Et_2O (2 × 20 mL). The combined organic phase was washed with H_2O (50 mL) and brine (50 mL) and dried (Na_2SO_4). Removal of the solvent gave the crude product as a brown oil, which was purified by flash chromatography on SiO_2 (Et_2O/hexane (1:1)) to yield **10** as a yellowish oil (4.26 g, 88%): IR (film) 3062, 2977, 2935, 1721, 1598, 1505, 1417, 1216, 1150, 1045, 978, 779, 752 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 3.43 (q, J = 7.1 Hz, 2H), 3.53 (q, J = 7.1 Hz, 2H), 7.24 (d, J = 8.7 Hz, 1H), 7.51 (td, J = 7.5, 1.1 Hz, 1H), 7.69 (td, J = 7.7, 1.5 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.7 Hz, 1H); MS (EI, 70 eV) *m/z* 244 (18, M^+), 227 (17), 145 (27), 128 (30), 116 (36), 100 (100), 72 (80).

***N*-(*N,N*-Diethylaminocarbonyl)-2-quinolone (11).** Short path distillation (173−175 °C/0.5 Torr) of 4.26 g of **10** yielded a mixture of **10** and a new product. Flash chromatography on SiO_2 (Et_2O) gave recovered **10** (2.39 g) and a colorless crystalline material (1.81 g), which upon recrystallization from $CHCl_3$/Et_2O (1:3) yielded pure **11** (1.07 g, 25%): mp 108.5−110 °C; IR (KBr) 2988, 2943, 2880, 1695, 1659, 1591, 1430, 829 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.2 Hz, 3H), 3.04−3.31 (m, 2H), 3.52−3.86 (m, 2H), 6.64 (d, J = 9.6 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.25 (td, J = 7.6, 1.0 Hz, 1H), 7.47−7.60 (m, 2H), 7.74 (d, J = 9.6 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 12.6, 13.7, 41.8, 43.4, 114.4, 119.9, 121.6, 123.1, 128.6, 131.0, 137.3, 140.7, 152.0, 160.2; MS (EI,

(33) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941.
(34) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 182.
(35) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69.
(36) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061.
(37) Mornet, R.; Gouin, L. *Synthesis* **1977**, 786.

70 eV) *m/z* 244 (18, M^+), 227 (9), 145 (12), 100 (100), 72 (67). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.75; H, 6.70; N, 11.48.

***N,N*-Diethyl 1,2-Dihydro-2-oxo-3-quinolinecarboxamide (12).** To a stirred LDA solution (diisopropylamine (592 mg, 5.9 mmol) and *n*-BuLi (3.9 mL (1.6 M in hexane), 6.2 mmol)) in THF (30 mL), a solution of **10** (1.10 g, 4.5 mmol) in THF (8 mL) (precooled to −78 °C) was added via cannula at −78 °C under N_2 atmosphere. After the solution was stirred for 1 h, anhydrous MeOH (562 mg, 17.5 mmol) was added and the reaction mixture was stirred for an additional hour at −78 °C. After quenching with saturated aq NH_4Cl (15 mL), the aqueous phase was extracted with $CHCl_3$ (3 × 30 mL). The combined organic phase was washed with H_2O and dried (Na_2SO_4). Removal of the solvent gave the crude product as yellow crystals (1.11 g). Flash chromatography on SiO_2 (EtOAc/MeOH (95:5)) yielded **12** as pale yellow crystals (666 mg, 61%): mp 166−167 °C (toluene) (lit.[31] mp 167 °C); IR (KBr) 3063, 2968, 2897, 1662, 1617, 1569, 1433, 1221, 946, 749 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, J = 6.6 Hz, 3H), 1.32 (t, J = 6.6 Hz, 3H), 3.34 (q, J = 6.8 Hz, 2H), 3.63 (q, J = 6.7 Hz, 2H), 7.24 (td, J = 7.5, 1.3 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.49−7.60 (m, 2H), 7.87 (s, 1H), 12.36 (s br, 1H, exchangeable with D_2O).

A second fraction was obtained and recrystallized from EtOAc/MeOH (2:1) to yield **13** as colorless crystals (122 mg, 13%): mp >180 °C dec; IR (KBr) 3063, 2974, 2938, 2892, 2853, 1718, 1658, 1619, 1591, 1564, 1399, 1275, 1196, 1080, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$/DMSO-d_6 (2:1)) δ 0.87 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H), 2.98−3.06 (m, 4H), 7.22 (t, J = 7.7 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.54−7.67 (m, 2H), 7.77−7.87 (m, 2H), 7.96 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 8.35 (s, 1H), 8.70 (s, 1H), 12.10 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$/DMSO-d_6 (2:1)) δ 11.1, 11.8, 39.3, 39.7, 113.7, 116.7, 120.7, 124.8, 125.1, 125.9, 126.7, 127.2, 127.8, 129.0, 130.0, 130.9, 138.7, 138.8, 141.2, 145.0, 150.7, 151.8, 158.5, 188.7.

***N,N*-Diethyl 2-Trifluoromethanesulfonyloxy-3-quinolinecarboxamide (7).** To a solution of **12** (441 mg, 2.0 mmol) in CH_2Cl_2 (18 mL) at 0 °C was added NEt_3 (365 mg, 3.6 mmol) and Tf_2O (560 mg, 2.0 mmol) dropwise under N_2 atmosphere. The solution was stirred at 0 °C for 1 h and quenched with saturated aq $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phase was washed H_2O and dried (Na_2SO_4). Removal of the solvent gave the crude product as yellow crystals (887 mg). Flash chromatography on SiO_2 (Et_2O) afforded **7** as pale yellow crystals (478 mg, 70%): mp 89.5−91 °C ($CHCl_3$/hexane (4:1)); IR (film) 3059, 2981, 2939, 1635, 1573, 1424, 1217, 1140, 1052, 918, 884, 847, 801, 759 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.12 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 3.25 (q, J = 7.1 Hz, 2H), 3.61 (s br, 2H), 7.67 (td, J = 7.5, 1.2 Hz, 1H), 7.84 (td, J = 8.4, 1.5 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 8.28 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.4, 13.9, 39.5, 43.1, 118.5 (q, 321), 122.6, 127.1, 127.8, 128.3, 128.6, 131.7, 139.0, 145.4, 149.6, 163.8; MS (EI, 70 eV) *m/z* 376 (36, M^+), 304 (100), 227 (49), 172 (82), 143 (66); HRMS calcd for $C_{15}H_{15}F_3N_2O_4S$ 376.0705, found 376.0693.

***N,N*-Diethyl 2-(2-Pyridyl)-3-quinolinecarboxamide (14).** A solution of 2-bromopyridine (117 mg, 741 μmol) in THF (3 mL) was treated at −78 °C with *t*-BuLi (1.7 M in pentane, 867 μL, 1.5 mmol) under N_2 atmosphere. After the dark red solution was stirred for 15 min at −78 °C, a solution of anhydrous $ZnBr_2$ (183 mg, 813 μmol) in THF (2 mL) was added via cannula. The resulting orange solution was stirred at −78 °C for 1 h and then allowed to warm to room temperature. A solution of **7** (185 mg, 492 μmol) and $Pd(PPh_3)_4$ (28 mg, 24 μmol) in THF (3 mL), which had been stirred for 15 min at room temperature, was added via cannula. The reaction mixture was refluxed (60 h) and quenched with saturated aq NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (1 × 20 mL, 2 × 10 mL) and the combined organic phase was washed with H_2O and dried (Na_2SO_4). Evaporation to dryness in vacuo gave the crude product as a brownish oil (208 mg), which was purified by flash chromatography on SiO_2 ($CHCl_3$) to yield **14** as a yellowish oil (85 mg, 57%): IR ($CDCl_3$) 3064, 2981, 2837, 2875, 1723, 1618, 1559, 1480, 1279, 1097 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 3.21 (s br, 2H), 3.93 (s br, 2H), 7.28−7.34 (m, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.72−7.87 (m, 3H), 8.14 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.42 (d, J = 7.9 Hz, 1H), 8.59 (s br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.7, 13.3, 38.7, 42.7, 123.1, 123.8, 127.0, 127.4, 127.5, 129.6, 130.1, 130.7, 134.8, 136.6, 147.3, 148.2, 153.4, 156.2, 170.3; MS (EI, 70 eV) *m/z* (305 (<1, M^+), 233 (100), 205 (19); HRMS calcd for $C_{19}H_{19}N_3O$ 305.1528, found 305.1500.

2-Bromo-6-methoxypyridine. A solution of NaOMe in MeOH (Na (1.33 g, 58 mmol) in anhydrous MeOH (14 mL)) was added to a suspension of 2,6-dibromopyridine (8.0 g, 34 mmol) in anhydrous MeOH (22 mL) and the resulting mixture was refluxed for 25 h. The reaction mixture was allowed to cool to room temperature, cold 5% aq $NaHCO_3$ (25 mL) was added, and the mixture was extracted with Et_2O (1 × 30 mL, 2 × 20 mL). The combined organic phase was concentrated, the resulting residue was taken up in Et_2O (30 mL), and the Et_2O solution was washed with brine (20 mL) and dried (K_2CO_3). Removal of the solvent gave a yellowish liquid (5.72 g). Kugelrohr distillation yielded 2-bromo-6-methoxypyridine as a colorless liquid (5.48 g, 86%): bp 87−91 °C/15 Torr (lit.[35] bp 85−95°/15 Torr); IR (film) 2985, 2952, 2850, 1594, 1581, 1556, 1467, 1408, 1296, 1020, 854 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.68 (d, J = 7.7 Hz, 1H), 7.05 (d, J = 7.4 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H).

***N,N*-Diethyl 2-(2-Methoxypyridin-6-yl)-3-quinolinecarboxamide (6).** To a solution of 2-bromo-6-methoxypyridine (301 mg, 1.6 mmol) in THF (6 mL) at −78 °C was added dropwise *t*-BuLi (1.7 M in pentane, 1.9 mL, 3.2 mmol) under N_2 atmosphere. The resulting pale yellow solution was stirred for 15 min at −78 °C. A solution of anhydrous $ZnBr_2$ (409 mg, 1.8 mmol) in THF (4 mL) was added via cannula and the mixture was stirred for 70 min at −78 °C. The reaction mixture was allowed to warm to room temperature and was added via cannula to a solution of **7** (399 mg, 1.1 mmol) and $Pd(PPh_3)_4$ (62 mg, 54 μmol) in THF (4 mL), which had been stirred for 20 min at room temperature. The resulting solution was refluxed for 45 h and the solvent was removed in vacuo. The residue was dissolved in $CHCl_3$/MeOH (9:1) (15 mL) and washed with $Na_2EDTA{\cdot}2H_2O$ (1.35 g in 15 mL of H_2O). The aqueous phase was extracted with $CHCl_3$/MeOH (9:1) (5 × 12 mL) and the combined organic phase was dried (Na_2SO_4). Removal of the solvent gave a yellow gum (569 mg) that was purified by flash chromatography on SiO_2 (EtOAc/hexane (2:1)) to give **6** as a pale yellow oil (211 mg, 59%): IR (film) 3060, 2979, 2934, 2874, 1634, 1574, 1556, 1267, 1047, 921, 888, 792 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.84 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 2.90−2.99 (m, 1H), 3.16−3.36 (m, 2H), 3.79−3.87 (m, 1H), 3.97 (s, 3H), 6.79 (d, J = 8.2 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 7.69−7.77 (m, 2H), 7.84 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 7.4 Hz, 1H), 8.17 (s, 1H), 8.18 (d, J = 5.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.8, 13.4, 38.9, 43.2, 53.7, 111.3, 116.3, 126.9, 127.4, 127.5, 129.5, 130.1, 130.3, 135.9, 139.2, 147.3, 153.4, 154.0, 163.4, 169.8; MS (EI, 70 eV) *m/z* 335 (7, M^+), 263 (100), 235 (23); HRMS calcd for $C_{20}H_{21}N_3O_2$ 335.1634, found 335.1602.

***N,N*-Diethyl 2-(2-Methoxypyridin-6-yl)-3-quinolinethiocarboxamide (15).** A solution of **6** (120 mg, 358 μmol) and Lawesson's reagent (241 mg, 596 μmol) in anhydrous benzene (3 mL) was refluxed for 8 h under N_2 atmosphere. The reaction mixture was passed through a cotton plug and the filtrate was concentrated. The resulting orange oil was purified by flash chromatography on SiO_2 (CH_2Cl_2/Et_2O (9:1)) to yield **15** as a yellow viscous liquid (105 mg, 83%): IR (film) 3064, 2982, 2941, 2876, 2221, 1592, 1575, 1498, 1266, 816 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (t, J = 7.2 Hz, 3H),

1.27 (t, J = 7.1 Hz, 3H), 3.25 (dq, J = 14.3, 7.1 Hz, 1H), 3.66 (dq, J = 14.3, 7.2 Hz, 1H), 3.95 (s, 3H), 4.03−4.19 (m, 2H), 6.78 (dd, J = 8.0, 0.6 Hz, 1H), 7.56 (td, J = 8.0, 1.0 Hz, 1H), 7.68−7.76 (m, 2H), 7.82 (dd, J = 8.1, 0.7 Hz, 2H), 8.09 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.1, 13.3, 45.9, 48.7, 53.9, 110.9, 117.3, 126.8, 127.4, 127.5, 129.2, 130.1, 134.3, 135.8, 139.1, 146.7, 152.2, 154.2, 163.2, 197.6; MS (EI, 70 eV) *m/z* 351 (25, M^+), 280 (47), 265 (100), 243 (12).

3-*N,N*-Diethylaminomethyl-2-(2-methoxypyridin-6-yl)-quinoline (16). To a solution of **15** (105 mg, 299 μmol) in anhydrous CH_2Cl_2 (1.5 mL) at 0 °C was added $Et_3O^+BF_4^-$ (0.5 M in CH_2Cl_2, 0.62 mL, 310 μmol) under N_2 atmosphere. The resulting mixture was stirred for 5 min at 0 °C and then for 90 min at room temperature. The solvent was removed in vacuo and the solid residue was dissolved in anhydrous MeOH (2.5 mL). $NaBH_4$ (29 mg, 767 μmol) was added at 0 °C and the mixture was stirred for 5 min at 0 °C and then for 3 h at room temperature. HCl (5%, 2 mL) was added and the mixture was stirred for 5 min. After addition of aq NaOH solution to pH >10, the reaction mixture was extracted with Et_2O (1 × 20 mL, 2 × 15 mL). The combined organic phase was washed with H_2O (20 mL) and dried (Na_2SO_4). Removal of the solvent gave a yellow oil (101 mg) that was purified by flash chromatography on SiO_2 (EtOAc) to yield **16** as a yellow gum (80 mg, 83%): IR ($CDCl_3$) 3064, 2971, 2935, 2874, 2809, 1722, 1576, 1464, 1411, 1261 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, J = 7.1 Hz, 6H), 2.54 (q, J = 7.1 Hz, 4H), 3.96 (s, 3H), 4.09 (s, 2H), 6.80 (dd, J = 8.4, 0.6 Hz, 1H), 7.49−7.55 (m, 2H), 7.64−7.77 (m, 2H), 7.86 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.53 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.8, 47.2, 53.4, 54.9, 110.2, 117.3, 126.6, 127.4, 127.9, 129.0, 129.2, 132.3, 136.7, 139.3, 156.8, 157.2, 162.7; MS (EI, 70 eV) *m/z* 321 (35, M^+), 292 (100), 249 (86), 235 (50), 205 (40), 185 (53); HRMS calcd for $C_{20}H_{23}N_3O$ 321.1841, found 321.1820.

11*H*-Indolizino[1,2-*b*]quinolin-9-one (5). To a suspension of anhydrous K_2CO_3 (23 mg, 166 μmol) and ClCOOEt (25 μL, 261 μmol) in anhydrous THF (1 mL) was added a solution of **16** (67 mg, 208 μmol) in anhydrous THF (1 mL) via cannula under N_2 atmosphere. The mixture was stirred at room temperature for 2.5 h. TLC showed a new spot with intense blue fluorescence under UV light. The reaction mixture was heated at reflux for 3 h. To the resulting orange suspension was added ClCOOEt (10 μL, 105 μmol) and the mixture was heated at reflux for 1 h. After the solution was cooled to room temperature, H_2O (10 mL) was added and the whole was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried (Na_2SO_4). Removal of the solvent gave a yellow solid (48 mg) that was purified by flash chromatography on SiO_2 (EtOAc/NEt_3 (99:1)) to yield **5** as pale yellow crystals (30 mg, 62%) (lit.[27a] mp 265 °C; lit.[27c] mp 253−254 °C): IR ($CDCl_3$) 3056, 1663, 1594, 1159 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.25 (s, 2H), 6.73 (dd, J = 9.0, 0.7 Hz, 1H), 7.30 (dd, J = 6.1, 0.8 Hz, 1H), 7.60−7.70 (m, 2H), 7.80 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 8.34 (s, 1H). The spectroscopic properties are identical with those reported for **5** prepared previously.[27]

Acknowledgment. This paper is dedicated with respect and in friendship to Professor Yuichi Kanaoka, a heterocyclic chemist par excellence. This work was supported by an NSERC Strategic Grant in collaboration with SmithKline Beecham. We thank Dr. J. Fortunak (now at Abbott Laboratories) for passionate interest and many stimulating discussions.

Supporting Information Available: Spectroscopic information and reagent purification and availability. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049890H